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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,691	08/29/2000	Gregg B. Fields	110.00680101	3203

7590 01/02/2002

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/02/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/529,691	Applicant(s) FIELDS ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The amendment filed on August 29, 2000 in Paper No. 6 is acknowledged and has been entered. Claim 19 has been amended. Claims 20 and 21 have been added.

2. The amendment filed on September 14, 2000 in Paper No. 7 is acknowledged and has been entered.

3. The amendment filed on May 4, 2001 in Paper No. 9 is acknowledged and has been entered.

4. Claims 1021 are pending in the application and are currently under prosecution.

Claim Objections

5. Claims 4 and 14 are objected to because the claims recite an amino acid sequence of fifteen residues, but do not refer to the sequence identification number(s) corresponding to the matching sequence(s) in the Sequence Listing and therefore fail to meet the requirements of 37 CFR §§ 1.821 – 1.825. Therefore, the communication filed May 4, 2001 is not fully responsive to the Office communication mailed March 29, 2001. The reason(s) for the lack of compliance to the Sequence Rules are reiterated on the attached Notice To Comply With The Sequence Rules. Applicants must comply with the requirements of the sequence rules (37 CFR §§ 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 6-8 and 16-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 1 and optionally conjugated to either a polyethylene glycol molecule or to a C_{10} alkyl molecule to partially inhibit binding of human melanoma cells to type IV collagen *in vitro*, to partially inhibit invasion of MATRIGEL by human melanoma cells *in vitro*, and to partially inhibit formation human melanoma foci in an experimental mouse model of metastasis, wherein the melanoma cells are pre-incubated with the polypeptide before injection into the mouse, does not reasonably provide enablement for the use of any polypeptide of claim 1 to inhibit the binding, invasion, or metastasis of any tumor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because in the absence of working exemplification that is commensurate in scope with the claims, one skilled in the art would not be able to practice (i.e., make and/or use) the claimed invention with a reasonable expectation of success without first having to perform extensive and undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

One cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human

clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs).

Although the teachings of Bergers, et al (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger, et al. Bergers, et al teach, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers, et al, disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers, et al also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical composition purported to have a desired pharmacological effect to a subject. The efficacy of any unproven drug must be determined empirically and such empirical determinations must be commensurate in scope with its expected and indicated uses.

Additionally, in view of the high level of unpredictability in the art, one skilled in the art would not accept the assertion that any polypeptide having an amino acid sequence that is a fragment of the continuous collagenous region of the major triple helical domain of the $\alpha 1$ chain of type IV collagen can be used to inhibit tumor cell adhesion, invasion, or metastasis based only upon the disclosed examples. Furthermore, one skilled in the art would not accept the assertion that any polypeptide having an amino acid sequence that is a fragment of the continuous collagenous region

of the major triple helical domain of the α1 chain of type IV collagen, including the peptide of SEQ ID NO: 1, can be used to inhibit the adhesion, invasion, or metastasis of any type of tumor cell based only upon the disclosed examples. In this regard and reminiscent of the teachings of Berger, et al (cited supra), it is noted that Nomizu, et al (*Journal of Biological Chemistry* **267**: 14118-14121, 1992) teaches that a peptide derived from laminin, which is a protein also involved in mediating tumor cell adhesion, actually promotes the growth of tumors in a mouse model for studying means for treating human melanoma (abstract). Again, as stated above, one skilled in the art cannot predict the effect of administering a pharmaceutical composition comprising the claimed polypeptide, which is purported to have a desired pharmacological effect to a subject, and would necessarily have to first perform extensive and undue experimentation in order to practice the claimed invention with a reasonable expectation of success. Therefore, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph.

7. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a polypeptide having an amino acid sequence that is a fragment of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen. However, the written description does not include a precise definition of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen. Furthermore, the written description does not include the amino acid sequence of residues 1263 through 1277 of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen. Accordingly, one cannot visualize or recognize the subject matter of the claimed invention. Moreover, one could not distinguish the members of the claimed genus of polypeptides from those fragments of type IV collagen that are not. Therefore, the

disclosure fails to meet the written description requirement of 35 USC § 112, first paragraph.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-4, 12-14, and 16-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4 and 12-14 are indefinite because claims 2 and 12 recite the phrase "corresponds substantially". Because the term "corresponds" is not defined in the specification or the claims, recitation of the phrase renders the claims indefinite because it cannot be ascertained whether the claims require the polypeptide or fragment thereof to be identical to a portion of the amino acids residues 1263 through 1277 of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen or merely to be similar. Furthermore, the claims are indefinite because "substantially" is relative term and the specification does not provide a standard for ascertaining the requisite degree to which the amino acid sequence of the polypeptide or fragment thereof must correspond to amino acids residues 1263 through 1277 of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 3, 4, 13, and 14 are vague and indefinite because claims 3 and 13 recite the limitation "where appropriate". Recitation of the limitation renders the claims vague and indefinite because it is unclear to what extent of incorporation of D-form amino acids in the polypeptide is deemed appropriate and the specification does not provide a standard for ascertaining the requisite degree of appropriateness. Furthermore, since claim 3 depends from claim 1, which requires the polypeptide to be in the "all D-form", use of the limitation "where appropriate" is particularly confusing and it is questionable as to whether claim 3 properly limits the subject matter of claim 1 as required under 35

USC § 112. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 16-21 are indefinite because claims 16-18 do not recite a positive process step that clearly relates back to the preamble of the claim. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claims to recite, for example, in the case of claim 16, the phrase "whereby binding of the tumor cell to type IV collagen is inhibited" at the end of the last line of the claim can obviate this rejection.

Claims 17, 18, 20, and 21 are indefinite because claims 17 and 18 recite the term "modulating". While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "modulating" in claims 17 and 18 is used by the claim to mean "bringing the polypeptide or peptide-conjugate in close proximity to, and preferably so close that it is contact with, the tumor cell" (page 5, lines 11-13) while according to The American Heritage® Dictionary of the English Language: Fourth Edition, 2000 the accepted meaning is: "To adjust or adapt to a certain proportion; regulate or temper." Therefore, in the context of the claim, according to the accepted meaning of the term "modulate", the method should comprise the step wherein a discernable or measurable property or attribute of the tumor cell is adjusted, adapted, regulated, or tempered by the polypeptide or polypeptide-conjugate. In view of the unusual meaning, which Applicants have afforded the term "modulating", the claims are indefinite and therefore one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Knutson, et al (*Proceedings of the American Association for Cancer Research* **36**: 68, Abstract No. 407, 1995).

Knutson, et al teach a polypeptide having an amino acid sequence that is a fragment of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen, wherein the fragment consists of the amino acid sequence contained in the segment spanning position 1263 through position 1277 of said continuous collagenous region and wherein the polypeptide is in the all D-form.

All the limitations of the claims are met.

12. Claim 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,082,926-A.

US Patent No. 5,082,926-A teaches a polypeptide having an amino acid sequence that is a fragment of the continuous collagenous region of the major triple helical domain of the α1 chain of type IV collagen, wherein the fragment consists of the amino acid sequence contained in the segment spanning position 1263 through position 1277 of said continuous collagenous region (abstract). US Patent No. 5,082,926-A also teaches that the polypeptide can be conjugated to a non-peptide moiety, namely a radioisotope, which is cytotoxic, by formation of a covalent bond between the polypeptide and the non-peptide moiety (column 6, lines 27-61).

All of the limitations of the claims are met.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,082,926-A. Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 1 and 2 of the patent encompass the subject matter of claims 1-15 of the instant application and because in light of the patents specification, it would have been *prima facie* obvious to one of ordinary skill in the art to use the polypeptides to inhibit tumor cell binding to type IV collagen, inhibit tumor cell invasion of a basement membrane, and/or to inhibit tumor cell metastasis.

Conclusion

15. No claims are allowed.

16. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. With the exception of US Patent No. 6,274,704-A, Applicants have provided the citations in the PTO Form-1449, which was filed on September 14, 2000 in Paper No. 7. These references are deemed pertinent to the Applicants' disclosure and are referred to here in the event that the references be used as the basis of a rejection under 35 USC §§ 102 or 103 in the subsequent Office Action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 17, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	09/529,691	FIELDS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Claims 4 and 14 recite an amino acid sequence, which is of sufficient length to be encompassed by the Sequence Rules under 37 CFR 1.821-1.825, but which are not properly identified by the sequence identification number(s) corresponding to the matching sequence in the Sequence Listing. If necessary, Applicant is required to submit a substitute copy of the CRF and paper copies of the Sequence Listing together with a statement indicating that no new matter is included in either copy and that both the CRF and paper copies are the same.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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Part of Paper No. 10